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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,365	BOOM ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *40-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39 and 58-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-39 and 58-73, in the response filed on 1/12/2006 is acknowledged. Claims 40-57 are withdrawn from further consideration. It is also noted for the record, as indicated in the attached interview summary form PTO-413, that the examiner has withdrawn the requirement for election of species issued in the previous Office Action entered 12/12/2005.

Claim Interpretation

The phrase "determining sequence variations" in the claims is interpreted to mean discerning the actual sequence of the biomolecule in question, and not the mere determination that a sequence variation exists. This interpretation is made in light of the specification, and includes either or both of an *actual* determination of the sequence of the biomolecule and a *prediction* of the sequence of the biomolecule.

Claim Rejections - 35 USC § 112 –2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 recites the limitation "in the target nucleic acid molecule" in referring to claim 1. There is insufficient antecedent basis for this limitation in the claim, as claim 1 is directed to a biomolecule, and does not specifically mention nucleic acid.

Claim Rejections - 35 USC § 112 – Enablement

Claims 1-39 and 58-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining sequence variations in nucleic acids and proteins for which some prior knowledge of possible sequence variation exists, does not reasonably provide enablement for determining sequence variations in any biomolecule or in cases where no prior knowledge of sequence variations exists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to methods of determining sequence variations in target biomolecules. The invention is the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass determining sequence variations in any molecule from any living organism. This would include any molecule for which the term "sequence" has any relevant meaning, such as lipids, polysaccharides, lipoproteins, lipooligosaccharides and glycoproteins.

Quantity of Experimentation

To practice the invention to the full extent of its claimed scope requires the ability to determine the sequence of any target biomolecule (i.e. to serve as a "reference biomolecule; see claim 1, step (b)), the ability to specifically cleave said target biomolecule (see claim 1, step (a)), and prior knowledge of what variations in the sequence are to be expected, as stated in paragraph [0112] of the specification:

> "As used herein, sequence variation order k refers to the sequence variation candidates of the target sequence constructed by the techniques provided herein, where the sequence variation candidates contain at most k mutations, polymorphisms, or other sequence variations, including, but not limited to, sequence variations between organisms, insertions, deletions and substitutions, in the target sequence relative to a reference sequence. The value of k is dependent on a number of parameters including, but not limited to, ***the expected type and number of sequence variations between a reference sequence and the target sequence***..." (emphasis added)

In cases where no prior knowledge of possible sequence variations exists, undue experimentation would be required to acquire such knowledge. For example, a large number of individuals from the population would need to be sampled, the sequences of a particular biomolecule determined, and comparisons made in order to identify a new sequence variation.

In addition, the Applicants' method depends on the ability to specifically cleave the target biomolecule. While Applicants have taught how this could be achieved for

nucleic acids and proteins, no such methods are taught for the specific cleavage of other biomolecules, such as polysaccharides or lipids.

The unpredictability of the art and the state of the prior art

Methods are taught in the disclosure and are known in the prior art for specific cleavage of nucleic acids, for example, with base-specific chemicals or enzymes such as the various RNases recited in the disclosure, as well as restriction endonucleases for cleaving DNA. Proteins can be cleaved after specific amino acid residues by chemicals or enzymes such as trypsin, for example.

In addition, the state of the art in mass-spectometry-based analysis of nucleic acids has been commented on by Zabeau et al (WO 00/66771, 2000):

> "Some of the MS-based assays have been used for the scoring of defined mutations or polymorphisms. Other processes derive multiple oligonucleotide fragments and yielda'mass-fingerprint'so as to analyze a larger target nucleic acid region for mutations and/or polymorphisms. The latter MS analyses are however considerably less informative in that they are essentially restricted to the detection of sequence variations. The methods cannot be applied to diagnostic sequencing of nucleic acids, where the term diagnostic sequencing means the unequivocal determination of the presence, the nature and the position of sequence variations. **At best, the measurements confirm the base composition of small fragments whose masses are determined with sufficient accuracy to reduce the number of possible compositional isomers.** Also, it will be realized that only certain changes in composition (as revealed by shifts in the mass spectrum) can be unambiguously assigned to a polymorphism or mutation. **A match between the spectrum of the interrogated sequence and a reference-spectrum obtained from wild-type sequence or sequences known to contain a given polymorphism, is assumed to indicate that the interrogated nucleic acid region is wild-type or incorporates the previously known polymorphisms, thereby disregarding certain other possible interpretations.**" (page 4, emphasis added)

This statement reaffirms that the methods of Applicants' invention are only enabling with regard to sequences for which prior knowledge of possible sequence variations exists.

Working Examples

The specification contains examples of base-specific fragmentation of RNA and DNA and subsequent analysis by mass spectrometry.

Guidance in the Specification.

There is adequate guidance in the specification for applying the claimed methods to RNA or DNA to determine the presence of sequence variations in a target nucleic acid and for predicting what the sequence of the variant molecule is. There is a general suggestion for the application of this method to proteins. There is no guidance with regard to any other biomolecules.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Given that the claims as written broadly encompass not only *predicting* the sequence of the variant molecule, but also determining the *actual* sequence of the molecule, the unpredictability of the art and state of the prior art, as well as indications in the specification itself which assumes prior knowledge of sequence variations on the part of the practitioner, one of skill in the art could not use the methods as claimed to determine or predict sequence variation in any target biomolecule. Additionally, the lack of guidance or working examples in the specification for biomolecules other than nucleic acids or polypeptides would not enable one of skill in the art to practice the invention with more complex biomolecules, such as branched oligosaccharides or lipids. Therefore the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-7, 9-11, 13-22, 24, 58 and 69-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Zabeau et al (WO 00/66771).

Regarding claims 1, 11 and 65, Zabeau teaches a method comprising: *(a) cleaving the target biomolecule into fragments by contacting the target biomolecule with one or more specific cleavage reagents* (See page 7, lines 13-21, reproduced below.); *(b) cleaving or simulating cleavage of a reference biomolecule into fragments with the same cleavage reagent* (See page 7, lines 13-21, reproduced below.); *(c) determining mass signals of the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(d) determining differences in the mass signals between the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(e) determining a reduced set of sequence variation candidates from the differences in the mass signals and thereby determining sequence variations in the target compared to the reference biomolecule* (See page 7, lines 13-21, reproduced below. Note that the detection of a mass inherently defines a reduced set of sequence variation candidates,

i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass. Also, since the method as taught by Zabeau actually yields the sequence of the target molecule, his method by definition determines a reduced set of sequence variation candidates, i.e. a set with one "candidate"):

> "In one embodiment, the present invention is directed to methods for sequence analysis of one or more target nucleic acids for which a known reference nucleic acid sequence is available. In this method, one or more target nucleic acids are derived from one or more biological samples, and a reference nucleic acid are each subjected to complementary cleavage reactions, and the products of the cleavage reactions are analyzed by mass spectroscopic methods. The mass spectra of the one or more target nucleic acids are then compared with the mass spectra of the reference nucleic acid sequence, and the nucleotide sequence of the one or more target nucleic acids is deduced by systematic computational analysis."

Zabeau also teaches SNP detection (page 15, lines 1-5), an additional limitation of claim 65.

With regard to claims 2, 4-6, and 68 Zabeau teaches a method in which the target molecules is "selected from the group consisting of a single stranded DNA, a double stranded DNA, a cDNA, a single stranded RNA, a double stranded RNA, a DNA/RNA hybrid, and a DNA/RNA mosaic nucleic acid" (page 7, lines 27-30).

With regard to claims 7 and 71, Zabeau teaches scoring sequence variations (page 10, lines 14-24 and page 33 line 5 through page 34 line 23).

With regard to claims 9, 10, 13 and 14, Zabeau teaches mass spectroscopy as the means for detecting mass differences in nucleic acid fragments (see entire document, especially page 9, lines 24-29) and that signals are manifest, for example, as missing or additional signals (page 19, lines 17-19).

With regard to claims 15-17, Zabeau teaches detection of SNPs (for example, page 5, lines 16-18). SNPs are by definition nucleotide substitutions.

With regard to claims 18 and 19, Zabeau teaches use of the methods with nucleic acids from prokaryotes (bacteria), eukaryotes (plants, animals, fungi) and viruses (page 34, lines 26-28).

With regard to claim 20, Zabeau specifically mentions Mycobacteria (page 36, lines 4-6).

With regard to claims 21, 22, 66 and 67, Zabeau teaches G-specific T_1 ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin (page 9, lines 18-21).

With regard to claim 24, Zabeau teaches genotyping (page 5 lines 28-29 and see example 5).

With regard to claim 58, Zabeau teaches modification to alter cleavage specificity (page 9, lines 1-10).

With regard to claim 69, Zabeau teaches target nucleic acids produced by transcription (page 8, lines 9-26).

With regard to claim 70, Zabeau teaches genome-wide discovery and scoring of SNPs useful as markers in genetic linkage studies (page 5, lines 16-18). While Zabeau does not explicitly teach the use of DNA from a single individual, the instruction to use SNPs for linkage analysis provides an implicit teaching to use DNA from a single individual. Chapter 2144.01 states:

> " '[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.' *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968)"

One of skill in the art would infer that Zabeau teaches using genomic DNA from an individual for SNP-based linkage analysis, because such an analysis would yield meaningless results if performed with genomic DNA pooled from multiple individuals.

With regard to claims 71-73, Zabeau teaches determining SNPs further comprising scoring heterozygosity (see page 50, example 5). Although Zabeau does not specificly state scoring homozygosity, there is an implicit teaching of such, especially since Zabeau states: "a single specific cleavage reaction may often suffice for both allele and **zygosity** identification" (emphasis added). One of skill in the art would reasonably infer zygosity refers to both homozygosity as well as heterozygosity. See MPEP 2144.01 for a discussion of implicit disclosure.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Chait et al (USPN 6,271,037).

Regarding claims 1-3, Chait teaches a method of determining sequence variation in a target biomolecule comprising: *(a) cleaving the target biomolecule into fragments by contacting the target biomolecule with one or more specific cleavage reagents* (See column 9 line 62 through column 10 line 16, and column7 line 64 through column 8 line 13. The "target biomolecule" is the phosphorylated form of the peptide of SEQ ID NO:10. The specific cleavage agent is the acid, which cleaves only the N-terminal residue which has been modified with PITC; see figure 3.); *(b) cleaving or simulating cleavage of a reference biomolecule into fragments with the same cleavage reagent* (See column 9 line 62 through column 10 line 16, and column7 line 64 through column 8

line 13. The "reference biomolecule" is the unphosphorylated form of the peptide of SEQ ID NO:10.); *(c) determining mass signals of the fragments produced in (a) and (b)* (See column 9 line 62 through column 10 line 16, especially lines 1-6 of column 10.); *(d) determining differences in the mass signals between the fragments produced in (a) and (b)* (See column 10 lines 8-12, and see figure 13A and B.); *(e) determining a reduced set of sequence variation candidates from the differences in the mass signals and thereby determining sequence variations in the target compared to the reference biomolecule* (See column 10 lines 8-12, and see figure 13A and B. Note that the detection of a mass inherently defines a reduced set of sequence variation candidates, i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass. In this case: "This measured mass difference corresponds to a phosphorylated serine residue" (column 10, lines 12-14)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 12, 26-32, 34-39 and 59-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771).

Regarding claims 8, 12, 29, 35, and 59, Zabeau teaches a method comprising: *(a) cleaving the target biomolecule into fragments by contacting the target biomolecule with one or more specific cleavage reagents* (See page 7, lines 13-21, reproduced below.); *(b) cleaving or simulating cleavage of a reference biomolecule into fragments with the same cleavage reagent* (See page 7, lines 13-21, reproduced below.); *(c) determining mass signals of the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(d) determining differences in the mass signals between the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(e) determining a reduced set of sequence variation candidates from the differences in the*

mass signals and thereby determining sequence variations in the target compared to the reference biomolecule (See page 7, lines 13-21, reproduced below. Note that the detection of a mass inherently defines a reduced set of sequence variation candidates, i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass. Also, since the method as taught by Zabeau actually yields the sequence of the target molecule, his method by definition determines a reduced set of sequence variation candidates, i.e. a set with one "candidate"):

> "In one embodiment, the present invention is directed to methods for sequence analysis of one or more target nucleic acids for which a known reference nucleic acid sequence is available. In this method, one or more target nucleic acids are derived from one or more biological samples, and a reference nucleic acid are each subjected to complementary cleavage reactions, and the products of the cleavage reactions are analyzed by mass spectroscopic methods. The mass spectra of the one or more target nucleic acids are then compared with the mass spectra of the reference nucleic acid sequence, and the nucleotide sequence of the one or more target nucleic acids is deduced by systematic computational analysis."

Zabeau also teaches applying the method to a plurality of nucleic acid molecules (page 5, lines 10-15), a mixture (i.e. pooled) of nucleic acids (page 5, lines 10-15) with more than one specific cleavage reaction (page 6, lines 20-27), and SNP detection (page 15, lines 1-5), which are additional limitations of claims 29, 35, and 59, respectively, of the instant application.

With regard to claim 62 Zabeau teaches a method in which the target molecules is "selected from the group consisting of a single stranded DNA, a double stranded DNA, a cDNA, a single stranded RNA, a double stranded RNA, a DNA/RNA hybrid, and a DNA/RNA mosaic nucleic acid" (page 7, lines 27-30).

With regard to claims 29, 35, and 59, Zabeau teaches scoring sequence variations (page 10, lines 14-24 and page 33 line 5 through page 34 line 23).

With regard to claims 32, 60, and 61, Zabeau teaches G-specific T_1 ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin (page 9, lines 18-21).

With regard to claims 26-28, see page 47 line 11 through page 48 line 13. Zabeau detects alleles with frequencies ranging from 5-10% and contemplates lower (i.e. less than 5%) detection limits.

With regard to claims 30, 31 and 34, Zabeau teaches applying the cleaved nucleic acid molecules to an array, specifically the onto a Spectrochip™ (Sequenom Inc., San Diego, CA) for analysis by MALDI-TOF-MS (see page 43, lines 22-25). As evidenced by the enclosed specification sheet for the Spectrochip™, this comprises an array as defined in paragraph [0314] of the specification.

With regard to claim 36, Zabeau teaches analysis of nucleic acid from tumor samples (page 6 lines 5-7).

With regard to claims 37 and 64, Zabeau teaches using nucleic acids pooled from individuals for genomic sequence analysis (page 6 lines 7-10).

With regard to claim 63, Zabeau teaches target nucleic acids produced by transcription (page 8, lines 9-26).

The only limitations Zabeau **does not teach** are:

(1) The limitation expressed in claims 8, 12, 29, 35 and 59 of, as stated in claim 8, *determining compomers corresponding to the different fragments…that are*

compomer witnesses; and...determining a reduced set of sequence variation candidates corresponding to the compomer witnesses.

(2) The limitations expressed in claims 38 and 39 regarding the percentage of the mixture of target nucleic acids that contain the sequence variation.

With regard to the first limitation (regarding compomers, etc.), while Zabeau does not incorporate this step into the preferred ch that mass spectroscopy-based assays are small fragments whose masses are determi number of possible compositional isomers" (Applicant's definition of "compomer", "compo e variation candidates" found in paragraphs [01(e specification.

↑ Question 2

Therefore, it would have been *prima faci* ..dinary skill in the art at the time the invention of the instant application was made to modify the method of Zabeau to incorporate the optional step taught by Zabeau of determining the base composition to reduce the number of possible compositional isomers (i.e. compomers). One of skill in the art would have been motivated to do this in cases where known polymorphisms were being assessed, because this would require fewer cleavage reactions than would be required for the actual *unequivocal* determination of the sequence of the target. This modification would in turn simplify the assay as well as reduce the time and expense of the assay.

With regard to the second limitation (of claims 38 and 39 regarding the percentage of a mixed sample of nucleic acids that contains a sequence variation), Zabeau teaches analysis of nucleic acid from tumor samples (page 6 lines 5-7). Zabeau also teaches, on page 47 line 11 through page 48 line 13, that his method detects alleles in mixed samples with frequencies ranging from 5-10% and contemplates lower (i.e. less than 5%) detection limits. Zabeau does not specifically teach the use of his method to detect a mutant allele in a mixed sample obtained from a tumor sample, wherein the mutant allele comprises a specific percentage.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the method taught by Zabeau to detect a sequence variation, as taught by Zabeau, wherein the frequency of the mutant allele in the sample was less than 5%. One would have been motivated to do so because Zabeau teaches that detection of allele frequencies of less than 5% is desirable. In addition, Zabeau teaches on page 6, lines 4-7 that using his methods "such sequences or sequence variants can be analyzed even when present as a lesser species. This is a *useful quality for the analysis of clinical samples which are often genetically heterogeneous* because of the presence of both normal and diseased cells or in itself (e.g., *cancerous tissue*, viralquasi-species)" (emphasis added).

Claims 23 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771) as applied to claims 1 and 29 above, and further in view of McCarthy et al (WO 97/03210).

Zabeau teaches a method of determining sequence variation in a target biomolecule comprising: *(a) cleaving the target biomolecule into fragments by contacting the target biomolecule with one or more specific cleavage reagents* (See page 7, lines 13-21, reproduced below.); *(b) cleaving or simulating cleavage of a reference biomolecule into fragments with the same cleavage reagent* (See page 7, lines 13-21, reproduced below.); *(c) determining mass signals of the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(d) determining differences in the mass signals between the fragments produced in (a) and (b)* (See page 7, lines 13-21, reproduced below.); *(e) determining a reduced set of sequence variation candidates from the differences in the mass signals and thereby determining sequence variations in the target compared to the reference biomolecule* (See page 7, lines 13-21, reproduced below. Note that the detection of a mass inherently defines a reduced set of sequence variation candidates, i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass.):

> "In one embodiment, the present invention is directed to methods for sequence analysis of one or more target nucleic acids for which a known reference nucleic acid sequence is available. In this method, one or more target nucleic acids are derived from one or more biological samples, and a reference nucleic acid are each subjected to complementary cleavage reactions, and the products of the cleavage reactions are analyzed by mass spectroscopic methods. The mass spectra of the one or more target nucleic acids are then compared with the mass spectra of the reference nucleic acid sequence, and the nucleotide sequence of the one or more target nucleic acids is deduced by systematic computational analysis."

Zabeau does not teach using a glycosylase to effect specific cleavage of the target and reference biomolecules.

McCarthy teaches a method of achieving base-specific cleavage by introducing a modified base that is a substrate for a DNA glycosylase, excising the modified base using the DNA glycosylase to generate abasic sites, cleaving the phosphate linkages at the abasic sites, and analyzing the cleavage products produced (see abstract). McCarthy does not teach analyzing the cleavage products using mass spectrometry.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the base-specific cleavage of nucleic acid with glycosylase as taught be McCarthy in the method of nucleic acid analysis taught by Zabeau, because this would provide another art recognized means for achieving base-specific cleavage of nucleic acid.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771) as applied to claim 11 above, and further in view of Muller et al (2000).

Zabeau teaches all of the limitations of claim 11, upon which claim 25 depends, as discussed above. Zabeau does not teach the use of his methods to determine epigenetic changes in a target nucleic acid relative to a reference nucleic acid. Muller teaches the use of a mass-spectrometry-based method for analyzing the imprinting status of the *TSSC3* gene (see page 757, column 2, penultimate paragraph). Muller does not teach a method involving base-specific cleavage of a target nucleic acid (but rather a target-dependent primer extension).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to apply the method of Zabeau to the analysis of imprinting status as taught by Muller, because, as Muller states on page 757, 1st sentence of the *Introduction*, "Epigenetic alterations to gene function are important in tumorigenesis". Therefore, one would have been motivated to substitute Zabeau's method for the method of Muller to assess epigenetic changes, since both Muller's and Zabeau's methods were art-recognized equivalents for the purpose of identifying sequence variations in a target nucleic acid.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-39 and 58-73 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/933611. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications are drawn to methods of determining sequence variations comprising the steps of obtaining a target and reference molecules, cleaving in a specific manner the target and reference molecules (or simulating cleavage of the latter), analyzing the masses of the resulting fragments, comparing the two sets of data, determining a reduced set of sequence variation candidates, and thereby determining sequence variations in the target nucleic acid compared to the reference nucleic acid. Compare claim 4 of the instant application with claim 19 of application 10/933611. The only difference between the two is that where claim 4 of the instant application recites (in claim 1) "contacting the target biomolecule with one or more specific cleavage reagents", claim 19 of the '611 application recites (in claim 1) "fragmenting a target nucleic acid at a plurality of specific and predictable sites".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

JEFFREY FREDMAN
PRIMARY EXAMINER
3/3/06